# 2001 Consensus Guidelines for the Management of Women With Cervical Cytological Abnormalities

Thomas C. Wright, Jr, MD
J. Thomas Cox, MD
L. Stewart Massad, MD
Leo B. Twiggs, MD
Edward J. Wilkinson, MD
for the 2001 ASCCP-Sponsored Consensus Conference

**Objective** To provide evidence-based consensus guidelines for the management of women with cervical cytological abnormalities and cervical cancer precursors.

**Participants** A panel of 121 experts in the diagnosis and management of cervical cancer precursors, including representatives from 29 professional organizations, federal agencies, and national and international health organizations, were invited to participate in a consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology (ASCCP).

**Evidence and Consensus Process** Guidelines for the management of women with cervical cytological abnormalities were developed through a multistep process. Starting 6 months before the conference, working groups developed draft management guidelines based on formal literature reviews of English-language articles published in 1988-2001, as well as input from the professional community at large, obtained using interactive Internet-based bulletin boards. On September 6-8, 2001, the ASCCP Consensus Conference was held in Bethesda, Md. Guidelines with supporting evidence were presented and underwent discussion, revision, and voting.

**Conclusions** Management of women with atypical squamous cells (ASC) depends on whether the Papanicolaou test is subcategorized as of undetermined significance (ASC-US) or as cannot exclude high-grade squamous intraepithelial lesion (HSIL) (ASC-H). Women with ASC-US should be managed using a program of 2 repeat cytology tests, immediate colposcopy, or DNA testing for high-risk types of human papillomavirus (HPV). Testing for HPV DNA is the preferred approach when liquid-based cytology is used for screening. In most instances, women with ASC-H, low-grade squamous intraepithelial lesion, HSIL, and atypical glandular cells should be referred for immediate colposcopic evaluation.

*JAMA. 2002;287:2120-2129* www.jama.com

EACH YEAR APPROXIMATELY 50 million women undergo Papanicolaou testing in the United States.[1] Of these, approximately 3.5 million (7%) are diagnosed with a cytological abnormality requiring additional follow-up or evaluation.[2] Determining which women with cytological abnormalities are at risk for significant cervical disease, performing appropriate diagnostic workups, and treating cancer precursors present a major public health challenge.

There are a number of reasons why comprehensive, evidence-based guidelines are needed for the management of women with cervical cytological abnormalities. One reason is that a National Cancer Institute workshop recently revised the criteria used by cytologists to render certain cytological interpretations, as well as the terminology used for reporting cervical cytology results (ie, the Bethesda System).[3] Other reasons include a better understanding of the pathogenesis and natural history of human papillomavirus (HPV) and cervical cancer precursors, and the availability of data from the National Cancer Institute's randomized Atypical Squamous Cells of Undetermined Significance/Low-grade Squamous Intraepithelial Lesion (ASCUS/LSIL) Triage Study (ALTS) (D. Solomon, MD, written communication, September 6-8, 2001). Moreover, existing guidelines were developed before sensitive molecular methods for detecting high-risk types of HPV and liquid-based cytology methods became widely available. Data are now available suggesting that these new technologies, when used together, are attractive alternatives to older approaches for managing women with cer-

**See also pp 2114 and 2140.**

**Author Affiliations:** Department of Pathology, College of Physicians and Surgeons of Columbia University, New York, NY (Dr Wright); Student Health Services, University of California–Santa Barbara, and American Social Health Association, Durham, NC (Dr Cox); Department of Obstetrics and Gynecology, Cook County Hospital, Chicago, Ill (Dr Massad); Institute of Women's Health, University of Miami, Miami, Fla (Dr Twiggs); and Department of Pathology, University of Florida College of Medicine, Gainesville (Dr Wilkinson).
**A list of participating professional and health organizations and federal agencies** is located at the end of this article.
**Corresponding Author and Reprints:** Thomas C. Wright, Jr, MD, Department of Pathology, College of Physicians and Surgeons of Columbia University, Room 16-404, P&S Bldg, 630 W 168th St, New York, NY 10032 (e-mail: tcw1@columbia.edu).

tain types of cytological abnormalities (D. Solomon, MD, written communication, September 6-8, 2001).[4,5] As a result, there is increasing pressure on clinicians to begin using these technologies and a need for clear, unbiased guidelines delineating their best use.

From September 6 through 8, 2001, the American Society for Colposcopy and Cervical Pathology (ASCCP) hosted a consensus conference in Bethesda, Md, to develop evidence-based guidelines for the management of women with cervical cytological abnormalities and cervical cancer precursors. To ensure that the guidelines reflect the needs of the diverse array of clinicians providing cervical cancer screening, the consensus conference included representatives from 29 participating professional and health organizations and federal agencies. Input from the professional community at large was obtained using a novel approach that incorporated Internet-based discussion groups. This report provides a summary of the key recommendations from that meeting with respect to managing cytological abnormalities. Comprehensive discussion of the data supporting the recommendations, as well as guidelines for the management of biopsy-confirmed cervical cancer precursors, will be posted on the ASCCP Web site (http://www.asccp.org) when available.

## GUIDELINE-DEVELOPMENT PROCEDURES

The consensus conference included 121 invited participants. Six months before the conference, working groups began developing draft guidelines through a multistep process. Open Internet bulletin boards were used for discussing key issues and MEDLINE searches of English-language articles published between 1988 and 2001 were performed. Abstracts of articles were reviewed to determine their relevance; relevant articles were reviewed to determine whether they fulfilled a minimum, predetermined scientific standard. In instances in which published data pertaining to a key issue were missing, scant, or conflicting, expert opinions expressed on the Internet bulletin boards or by members of the working group were used to help formulate the guidelines. Draft guidelines were posted on the Internet bulletin boards for public comment. At the consensus conference, guidelines were discussed together with the supporting data, revised if necessary, and voted upon. All guidelines were accepted by a minimum of a two-thirds majority vote.

Each guideline is rated using a 2-part rating system (TABLE 1).[6,7] The letters A through E are used to indicate the "strength of recommendation" for or against the use of a particular option. Determination of the level of the evidence in the "strength of recommendation" (ie, good, moderate, or insufficient) was based on consideration of several criteria, including potential for harm if an intervention did not take place, the potential complications associated with an intervention, as well as the "quality of evidence." Therefore an exact correlation does not exist between the "quality of evidence" and the "strength of a recommendation." Roman numerals I through III are used to indicate the "quality of evidence." In addition, the terms "recommended," "preferred," "acceptable," and "unacceptable" were specifically defined at the consensus conference. These terms were used because in some clinical situations there are several treatment options that have good evidence of efficacy that supports clinical use; however, based on less-defined issues such as costs or patient convenience, one method might be "preferred."

## 2001 CONSENSUS GUIDELINES

The 2001 Consensus Guidelines are designed to assist in the management of women with cytological abnormalities and cervical cancer precursors. It is important to recognize that in many instances the amount and quality of data available to inform the decision-making process were limited. In such cases, guidelines had to be developed from a review of studies incorporating small numbers of cases or from consensus expert opinion. It is also impor-

**Table 1.** Rating System for Recommendations

| Rating | Criteria |
|---|---|
| | **Strength of Recommendation*** |
| A | Good evidence for efficacy and substantial clinical benefit support recommendation for use |
| B | Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use |
| C | Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds |
| D | Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use |
| E | Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use |
| | **Quality of Evidence*** |
| I | Evidence from at least 1 randomized controlled trial |
| II | Evidence from at least 1 clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 center), or from multiple time-series studies, or dramatic results from uncontrolled experiments |
| III | Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees |
| | **Terminology†** |
| Recommended | Good data to support use when only 1 option is available |
| Preferred | Option is the best (or one of the best) when there are multiple other options |
| Acceptable | One of multiple options when either there are data indicating that another approach is superior or when there are no data to favor any single option |
| Unacceptable | Good data against use |

*Modified from Kish[7] and from Gross et al.[89]
†The assignment of these terms represents an opinion or vote by the consensus conference, and the assignment is not directly linked to the "strength of evidence" or the "quality of evidence."

tant to recognize that these guidelines should never be a substitute for clinical judgment. Clinicians need to practice clinical discretion when applying a guideline to an individual patient since it is impossible to develop guidelines that apply to all situations.

The guidelines use the 2001 Bethesda System for cytological classification that uses the terms LSIL and HSIL to refer to cervical cancer precursors.[3] We have adopted a 2-tiered terminology for the histopathological classification of cervical intraepithelial neoplasia (CIN): CIN 1 denotes low-grade precursors and CIN 2,3 denotes high-grade precursors.[8] Detailed algorithms describing the 2001 Consensus Guidelines, and a glossary of terms used in the guidelines, are available at the ASCCP Web site (glossary also available at http://jama.ama-assn.org).

## ATYPICAL SQUAMOUS CELLS

The 2001 Bethesda System subdivides atypical squamous cells (ASC) into 2 categories: atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells, cannot exclude HSIL (ASC-H).[3] Several considerations underlie the consensus guidelines for the management of ASC. First, even among expert cytologists, the interpretation of a cervical cytology result as ASC is poorly reproducible.[9-11] Second, a woman with a cervical cytology result interpreted as ASC has a 5% to 17% chance of having CIN 2,3 confirmed by biopsy, while CIN 2,3 is identified in 24% to 94% of those with ASC-H.[5,12-20] However, the risk of invasive cervical cancer in a woman with ASC is low (approximately 0.1% to 0.2%).[21,22] These considerations suggest that a woman with ASC requires some form of additional workup or follow-up, but that consideration should be given to preventing unnecessary inconvenience, anxiety, cost, and discomfort. Immunosuppressed women with ASC are at increased risk for CIN 2,3, and high-risk types of HPV are frequently detected in immunosuppressed women, suggesting that these women require special consideration.[23,24] Conversely, postmenopausal women with ASC appear to be at lower risk for CIN 2,3 than premenopausal women.[14,25,26]

### Approaches to Managing Women With ASC

Repeating cervical cytological testing at specified intervals, performing immediate colposcopy, HPV DNA testing for high-risk types, or combining a single repeat cervical cytological test with another adjunctive method are all widely used in the United States for managing women with ASC. Each of these approaches has advantages and disadvantages.

Although repeat cytological testing is widely used for managing women with ASC, the sensitivity of a single repeat test for detecting CIN 2,3 is relatively low (0.67-0.85) (TABLE 2).[4,5,12,27-30] To compensate for this, previous guidelines have recommended that testing be repeated at specified intervals until a patient has several consecutive "negative for squamous intraepithelial lesion or malignancy" results before returning to routine screening.[31-33] The most appropriate threshold for referring women for colposcopy has been evaluated in several studies and appears to be a repeat cytology result of ASC or greater.[12,34,35] Referral thresholds of LSIL and HSIL miss many women with biopsy-confirmed CIN 2,3. There is limited information available on key parameters (eg, timing of the repeat test, number of repeats necessary) needed to design a program of repeat cytological testing. Repeating cervical cytological testing has several disadvantages compared with other management options. It can delay the diagnosis of CIN 2,3 or cervical cancer and, even in populations with good access to health care, adherence to recommendations becomes a problem for any follow-up that requires multiple visits.

The advantage of colposcopy for the evaluation of women with ASC is that it immediately informs both the woman and the clinician of the presence or absence of significant disease. A meta-analysis of the performance of colposcopy reported that the weighted mean sensitivity for distinguishing normal cervical tissue from abnormal tissue by colposcopy was 0.96 and the weighted mean specificity was 0.48.[36] However, since most published studies have been performed by expert colposcopists and have not uniformly obtained histological samples from normal-appearing tissue, the sensitivity of colposcopy in the published literature may be higher than would be observed in routine clinical practice. The disadvantages of colposcopy are that many women consider the procedure to be uncomfortable, referral for colposcopy may raise false con-

**Table 2.** HPV DNA Testing for the Management of Women With ASC*

| Source, y | Patients, No. | Repeat Cytology | | HPV DNA Testing | |
|---|---|---|---|---|---|
| | | Sensitivity (95% CI) | % Referred (95% CI) | Sensitivity (95% CI) | % Referred (95% CI) |
| Ferris et al,[28] 1998; Ferris et al,[35] 1998† | 144 | 0.70 (0.42-0.98) | 56 (49-64) | 0.89 (0.69-1.00) | 43 (35-51) |
| Manos et al,[4] 1999† | 995 | 0.76 (0.65-0.87) | 38 (35-41) | 0.89 (0.81-0.97) | 39 (36-42) |
| Bergeron et al,[27] 2000 | 111 | 0.67 (0.50-1.00) | 32 (23-41) | 0.83 (0.62-1.00) | 43 (34-52) |
| Lin et al,[29] 2000 | 74 | NA | NA | 1.00 | 53 (42-64) |
| Shlay et al,[30] 2000 | 200 | NA | NA | 0.93 (0.81-1.00) | 31 (25-37) |
| Solomon et al,[12]† | 2324 | 0.85 (0.81-0.89) | 59 (57-61) | 0.96 (0.94-0.98) | 56 (54-58) |

*DNA testing for high-risk types of human papillomavirus (HPV) was performed using the Hybrid Capture II HPV DNA Assay (Digene Inc, Gaithersburg, Md). ASC indicates atypical squamous cells; CI, confidence interval; and NA, not applicable.
†HPV DNA testing was performed from liquid-based cytology specimens.

cerns about cervical disease, it is expensive, and it has the potential for overdiagnosis and overtreatment.

Several large studies have evaluated the performance of DNA testing using commercially available, highly sensitive molecular methods to detect high-risk types of HPV for the management of women with ASC (Table 2). The sensitivity of HPV DNA testing for the detection of biopsy-confirmed CIN 2,3 in women with ASC is 0.83 to 1.0 and is higher than the sensitivity of a single repeat cervical cytological test (conventional or liquid-based) in all of the reported series. The negative predictive value of DNA testing for high-risk types of HPV is generally reported to be 0.98 or greater. Between 31% and 60% of all women with ASC will have high-risk types of HPV identified, but the proportion with high-risk HPV decreases with increasing age.[5,37] It is not known how to manage women who test positive for high-risk HPV DNA, but who turn out not to have CIN.

Requiring women to return for HPV DNA testing or repeat cervical cytological testing is inconvenient and would be expected to increase cost. "Reflex" HPV DNA testing is an alternate approach, in which the original liquid-based cytology specimens or a sample co-collected for HPV DNA testing at the initial screening visit is tested for HPV DNA only if an ASC-US result is obtained.[5] Reflex HPV DNA testing offers significant advantages since women do not need an additional clinical examination for specimen collection, and 40% to 60% of women will be spared a colposcopic examination. Moreover, women testing negative for HPV DNA can rapidly be assured that that they do not have a significant lesion.

## Recommended Management of Women With ASC-US

A program of repeat cervical cytological testing, colposcopy, or DNA testing for high-risk types of HPV are all acceptable methods for managing women with ASC-US (rating AI). When liquid-based cytology is used or when cocollection for HPV DNA testing can be done, reflex HPV DNA testing is the preferred approach (AI).

DNA testing for high-risk types of HPV should be performed using a sensitive molecular test, and all women who test positive for HPV DNA should be referred for colposcopic evaluation (AII). Women with ASC-US who test negative for high-risk HPV DNA can be followed up with repeat cytological testing at 12 months (BII). Acceptable management options for women who are positive for high-risk types of HPV, but who do not have biopsy-confirmed CIN, include follow-up with repeat cytological testing at 6 and 12 months with referral back to colposcopy if a result of ASC-US or greater is obtained, or HPV DNA testing at 12 months with referral back to colposcopy of all HPV DNA–positive women (BII).

When a program of repeat cervical cytological testing is used, women with ASC-US should undergo repeat cytological testing (either conventional or liquid-based) at 4- to 6-month intervals until 2 consecutive "negative for intraepithelial lesion or malignancy" results are obtained (AII). Women diagnosed with ASC-US or greater cytological abnormality on the repeat tests should be referred for colposcopy (AII). After 2 repeat "negative for intraepithelial lesion or malignancy" cytology tests are obtained, women can be returned to routine cytological screening programs (AII).

When immediate colposcopy is used to manage women with ASC-US, women who are referred for colposcopy and found not to have CIN should be followed up with repeat cytological testing at 12 months (BII). Women with ASC-US who are referred for colposcopy and found to have biopsy-confirmed CIN should be managed according the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities (Wright et al, unpublished data, 2001).

Because of the potential for overtreatment, diagnostic excisional procedures such as the loop electrosurgical excision procedure (LEEP) should not routinely be used to treat women with ASC in the absence of biopsy-confirmed CIN (EII).

## ASC-US in Special Circumstances

**Postmenopausal Women.** Providing a course of intravaginal estrogen followed by a repeat cervical cytology test obtained approximately a week after completing the regimen is an acceptable option for women with ASC-US who have clinical or cytological evidence of atrophy and no contraindications to using intravaginal estrogen (CIII). If the repeat test result is "negative for intraepithelial lesion or malignancy," the test should be repeated in 4 to 6 months. If both repeat cytological test results are "negative for intraepithelial lesion or malignancy," the patient can return to routine cytological screening, whereas if either repeat test result is reported as ASC-US or greater, the patient should be referred for colposcopy (AII).

**Immunosuppressed Women.** Referral for colposcopy is recommended for all immunosuppressed patients with ASC-US (BII). This includes all women infected with human immunodeficiency virus (HIV), irrespective of CD4 cell count, HIV viral load, or antiretroviral therapy.

**Pregnant Women.** It is recommended that pregnant women with ASC-US be managed in the same manner as nonpregnant women (BIII).

## Recommended Management of Women With ASC-H

The recommended management of women with ASC-H obtained using either conventional or liquid-based cervical cytology is referral for colposcopic evaluation (AII).

When no lesion is identified after colposcopy in women with ASC-H, it is recommended that, when possible, a review of the cytology, colposcopy, and histology results be performed (CIII). If the review yields a revised interpretation, management should follow guidelines for the revised interpretation; if a cytological interpretation of ASC-H is upheld, cytological follow-up at 6 and 12 months or HPV DNA testing at 12 months is acceptable (CIII). Women

who are found to have ASC or greater on their repeat cervical cytology tests or who subsequently test positive for high-risk HPV DNA should be referred for colposcopy.

## ATYPICAL GLANDULAR CELLS AND ADENOCARCINOMA IN SITU

The 2001 Bethesda System classifies glandular cell abnormalities less severe than adenocarcinoma into 3 categories[3]: atypical glandular cells, either endocervical, endometrial, or "glandular cells" not otherwise specified (AGC NOS); atypical glandular cells, either endocervical or "glandular cells" favor neoplasia (AGC "favor neoplasia"); and endocervical adenocarcinoma in situ (AIS).

The AGC category is associated with a substantially greater risk for cervical neoplasia than the ASC or LSIL categories.[38] Various studies have found that 9% to 54% of women with AGC have biopsy-confirmed CIN, 0% to 8% have biopsy-confirmed AIS, and less than 1% to 9% have invasive carcinoma.[21,38-44] The 2001 Bethesda System separated AGC NOS from AGC "favor neoplasia" because it was believed that these 2 categories represent women at different risk for having significant disease, either squamous or glandular. Although the risk of having a high-grade lesion in various studies overlap, studies from individual centers have usually reported a higher risk among women with AGC "favor neoplasia" than among those with AGC NOS. Biopsy-confirmed high-grade lesions including CIN 2,3, AIS, or invasive cancer have been found in 9% to 41% of women with AGC NOS compared with 27% to 96% of women with AGC "favor neoplasia."[21,38-48] The cytological interpretation of AIS is associated with a very high risk of a woman having either AIS (48%-69%) or invasive cervical adenocarcinoma (38%).[49,50]

### Approaches to Managing Women With AGC and AIS

**Initial Workup and Evaluation.** All 3 methods (ie, repeat cytology, colposcopy, and endocervical sampling) traditionally used to evaluate women with AGC or AIS have limitations. Screening cervical cytology has a sensitivity of only 50% to 72% for identifying glandular neoplasia, and CIN is the most common form of neoplasia identified in women with a cytological result of AGC.[38-44,51-54] Moreover, repeat cervical cytological testing has been shown to be less sensitive than colposcopy for detecting CIN 2,3 and glandular lesions in women with AGC.[52] This supports the inclusion of colposcopy in the workup of women with AGC. However, many cases of biopsy-confirmed AIS have had no observed colposcopic abnormalities, and even combinations of cytological testing and colposcopy can miss small endocervical adenocarcinomas and AIS localized in the endocervical canal.[55] Although the sensitivity of endocervical sampling for the detection of glandular neoplasia localized in the endocervical canal is not well defined, many cases of biopsy-confirmed AIS have had no colposcopic abnormalities and in some series endocervical sampling has detected glandular neoplasia that was missed at colposcopy.[52,55-57] Age is a key factor in determining the frequency and type of neoplasia found in women with AGC. There is a higher risk of CIN 2,3 and AIS in premenopausal women compared with postmenopausal women, and premenopausal women with AGC have a lower risk of endometrial hyperplasia or cancer.[44,58-60] Approximately half of women with biopsy-confirmed AIS have a coexisting squamous abnormality and therefore the presence of a coexisting squamous abnormality does not change the management of women with AGC or AIS.[61-63]

**Subsequent Workup and Evaluation of Women in Whom Lesions Are Not Identified.** Because of the poor sensitivity of colposcopy, cytology, and endocervical sampling for detecting glandular abnormalities, women with AGC who do not have cervical neoplasia detected at the initial workup continue to be at increased risk. Because the risk varies with the subclassification of AGC (ie, either NOS or "favor neoplasia"), the most appropriate form of follow-up depends on the specific subclassification of AGC. Women with AGC NOS who have a negative initial workup have been found in some studies to be at relatively low risk for having a missed significant lesion.[47] Therefore, some authors have recommended that these patients can be followed up with repeat cytological testing.[47,64] However, women who have persistent AGC are at high risk for significant glandular disease.[47,48] In some studies, women with a cytological result of AGC "favor neoplasia" or AIS who have a negative initial workup have been diagnosed subsequently with significant lesions, including invasive cancers.[39,44,52] Therefore, some authors have suggested that the risk of a significant lesion in such patients is too great to rely on repeat cervical cytological testing alone, and have suggested that a diagnostic excisional procedure be used in this situation to rule out a serious endocervical lesion.[47,64] Other studies have reported that thermal damage can preclude the assessment of margins in electrosurgical or laser conization specimens obtained from women being evaluated for glandular cytological abnormalities and have recommended that cold-knife conizations be used in this setting.[61,65] The management of glandular cytological abnormalities can be quite challenging and women with unexplained glandular cytological findings should be referred to a clinician experienced in the management of complex cytological situations.

### Recommendations for Managing Women With AGC or AIS

**Initial Evaluation.** Colposcopy with endocervical sampling is recommended for women with all subcategories of AGC, with the exception that women with atypical endometrial cells should initially be evaluated with endometrial sampling (AII). Endometrial sampling should be performed in conjunction with colposcopy in women older than 35 years with AGC and in younger women with AGC who have unexplained vaginal bleeding (AII). Colposcopy with endocervical sampling is also

recommended for women with a cytological test result of AIS. Management of women with initial AGC or AIS using a program of repeat cervical cytological testing is unacceptable (EII). Currently, there are insufficient data to allow an assessment of HPV DNA testing in the management of women with AGC or AIS (CIII).

**Subsequent Evaluation or Follow-up.** If invasive disease is not identified during the initial colposcopic workup, it is recommended that women with AGC "favor neoplasia" or endocervical AIS undergo a diagnostic excisional procedure (AII). The preferred diagnostic excisional procedure for women with AGC or AIS is cold-knife conization (BII). If biopsy-confirmed CIN (of any grade) is identified during the initial workup of a woman with AGC NOS, management should be according to the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities (Wright et al, unpublished data, 2001). If no neoplasia is identified during the initial workup of a woman with AGC NOS, it is recommended that the woman be followed up using a program of repeat cervical cytological testing at 4- to 6-month intervals until 4 consecutive "negative for intraepithelial lesion or malignancy" results are obtained, after which the woman may return to routine screening (BIII). If a result of either ASC or LSIL is obtained on any of the follow-up Papanicolaou tests, acceptable options include a repeat colposcopic examination or referral to a clinician experienced in the management of complex cytological situations (BIII).

## LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

In 1996 the median rate of occurrence of LSIL in the United States was 1.6%, but laboratories serving high-risk populations report LSIL rates as high as 7.7%.[2,66] Cytological grade is a relatively poor predictor of the grade of CIN that will be identified at colposcopy, and approximately 15% to 30% of women with LSIL on cervical cytology will have CIN 2,3 identified on a subsequent cervical biopsy.[21,22]

### Approaches to Managing Women With LSIL

Approaches that previously have been recommended for managing women with LSIL include repeat cytological testing or colposcopy. In some clinical settings, patients with LSIL are routinely followed up using cytology alone, without an initial colposcopic evaluation. The rationale for this is that the majority of women with LSIL have either no cervical lesion or CIN 1, the majority of which spontaneously regress without treatment or are completely excised with a cervical biopsy. However, follow-up cytological studies have usually had high rates of loss to follow-up, a 53% to 76% likelihood of abnormal follow-up cytology results requiring eventual colposcopy, and a small but real risk of delaying the identification of invasive cancers.[35,67-69] In contrast, referring all women with LSIL for colposcopy allows women with significant disease to be rapidly identified and would be expected to reduce the risk that women would be lost to follow-up. Disadvantages of colposcopy are those previously outlined for women with ASC, but they appear to be outweighed by the higher risk of abnormality in women with LSIL. Even in patients found to have biopsy-confirmed CIN 1, establishing a histopathologically confirmed diagnosis has merit since it allows a treatment plan to be developed based on knowledge of the patient's cervical lesion.

Several approaches, including HPV DNA testing and LEEP, do not appear to be useful for the initial management of women with LSIL. In the ALTS study, 83% of women referred for the evaluation of an LSIL cytology result tested positive for high-risk HPV types.[70] Receiver operator curve analysis evaluating the performance of HPV DNA testing for the detection of women with CIN 2,3 has reported a lower specificity at a given level of sensitivity among women being evaluated for LSIL, compared with those being evaluated for ASC.[5] Loop electrosurgical excision procedures to excise the transformation zone in women referred for an abnormal cervical cytology result, but in whom biopsy-confirmed CIN has not been documented, frequently fail to identify neoplasia.[71,72]

### Management of Women With LSIL but No Cervical Lesions

Relatively few studies have addressed the issue of how to manage patients with LSIL who have satisfactory colposcopic examinations but no cervical lesions. One study found that 47% of such women had CIN diagnosed on a subsequent LEEP specimen; in the ALTS study, a considerable number of these women with LSIL who had no CIN detected at their initial colposcopic evaluation were subsequently found to have biopsy-confirmed CIN 2,3 (D. Solomon, MD, written communication, September 6-8, 2001).[73] Endocervical sampling reduces the risk of missed endocervical lesions among these women, as well as among women with LSIL and unsatisfactory colposcopic examinations. However, other studies of women with LSIL and an unsatisfactory colposcopic examination have found that the risk of missing a significant lesion is relatively low if neoplasia is not identified at the initial evaluation.[74] One study of 29 patients with cytology-confirmed LSIL or with biopsy-confirmed CIN 1 who had an unsatisfactory colposcopy and underwent cone biopsy identified only 2 cases of CIN 2,3 on the conization specimen and no invasive cervical carcinomas.[74]

### Recommendations for Managing Women With LSIL

Colposcopy is the recommended management option for women with LSIL (AII). Subsequent management options depend on whether a lesion is identified, whether the colposcopic examination is satisfactory, and whether the patient is pregnant. The routine use of diagnostic excisional procedures such as LEEP or ablative procedures is unacceptable for the initial management of patients with LSIL in the absence of biopsy-confirmed CIN (DII).

**Satisfactory Colposcopy.** Endocervical sampling is acceptable for nonpregnant women with satisfactory colposcopic findings and a lesion identified in the transformation zone (CII), but it is preferred for nonpregnant women in whom no lesions are identified (BII). If biopsy, with or without endocervical sampling, fails to confirm CIN and the colposcopy is satisfactory, acceptable management options include follow-up with repeat cytological testing at 6 and 12 months with a referral for colposcopy if a result of ASC-US or greater is obtained, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive for a high-risk type of HPV (BII).

**Unsatisfactory Colposcopy.** Endocervical sampling is preferred for nonpregnant women with unsatisfactory colposcopic findings (BII). If biopsy fails to confirm CIN and the colposcopy is unsatisfactory, acceptable management options include follow-up with repeat cytological testing at 6 and 12 months with a referral for colposcopy if a result of ASC-US or greater is obtained, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive (BII).

Women with LSIL who are found to have biopsy-confirmed CIN should be managed according to the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities (Wright et al, unpublished data, 2001).

### LSIL in Special Circumstances

**Postmenopausal Women.** In postmenopausal patients, follow-up without initial colposcopy is an acceptable option using protocols of either follow-up with repeat cytological testing at 6 and 12 months with a threshold of ASC-US or greater for referral for colposcopy, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive (CIII).

A course of intravaginal estrogen followed by a repeat cervical cytology test approximately a week after completing the regimen is acceptable for women with LSIL who have clinical or cytological evidence of atrophy, with a referral for colposcopy if a result of ASC-US or greater is obtained and there are no contraindications to using intravaginal estrogen (CIII). If the repeat cervical cytology test result is "negative for intraepithelial lesion or malignancy," cytological testing should be repeated in 4 to 6 months. If both repeat cytology test results are "negative for intraepithelial lesion or malignancy," the patient can return to routine cytological screening, whereas if either repeat result is reported as ASC or greater, the patient should be referred for colposcopy (CIII).

**Adolescents.** In adolescents, an acceptable option is follow-up without initial colposcopy using a protocol of repeat cytological testing at 6 and 12 months with a threshold of ASC for referral for colposcopy, or of HPV DNA testing at 12 months with a referral for colposcopy if testing is positive for high-risk HPV DNA (CIII).

**Pregnant Women.** For the recommended management of pregnant women with a diagnosis of LSIL, see the "HSIL in Special Circumstances" section, below.

## HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A cytological diagnosis of HSIL is uncommon, accounting for only 0.45% of cytology interpretations in 1996.[2] Women with a cytological diagnosis of HSIL have approximately a 70% to 75% chance of having biopsy-confirmed CIN 2,3 and a 1% to 2% chance of having invasive cervical cancer.[2,58,75]

### Approaches to Managing Women With HSIL

A cytological result of HSIL identifies a woman at significant risk for having CIN 2,3 or invasive cancer; therefore, colposcopy with endocervical assessment has traditionally been considered the best approach to managing these patients.[31] Usually, a colposcopic evaluation will identify a high-grade cervical or vaginal lesion.[58,75,76] However, those women with HSIL in whom a high-grade cervical or vaginal lesion is not identified after colposcopy appear to be at considerable risk for having an undiagnosed CIN 2,3 lesion. In some studies, up to 35% of women with a biopsy diagnosis of CIN 1 and a cytological result of HSIL have been found, after additional workup, to have biopsy-confirmed CIN 2,3.[77,78] Therefore, additional steps are usually taken when a high-grade cervical or vaginal lesion is not identified in a woman with HSIL. One of the first steps that is often taken is to perform a careful review of the colposcopic findings, biopsy results, and initial cervical cytology results. Numerous studies have shown that cytopathologists and histopathologists frequently differ in their interpretation of both cytological and histological cervical abnormalities, and that such a review can sometimes resolve the discrepancy.[11,79-81]

Many colposcopists believe that a cytology test result of HSIL in a pregnant patient requires special consideration. Pregnancy accentuates both normal and abnormal colposcopic findings, and clinicians may not obtain appropriate cervical biopsies out of concern of increased bleeding.[82,83] Although cervical biopsy during pregnancy is associated with an increased risk of minor bleeding, it has not been associated with increased rates of major bleeding or pregnancy loss in the large studies, and a failure to perform cervical biopsies in pregnant women has been associated with missed cancers.[84] Because of the risk of potential injury to the fetus, endocervical sampling is proscribed during pregnancy.

The approach of managing nonpregnant women with HSIL by immediate LEEP of the transformation zone (ie, "see and treat") has been shown to be safe, efficacious, and cost-effective, particularly in the hands of expert colposcopists.[85-88] However, most studies of women undergoing immediate LEEP for cytological abnormalities have reported that a significant number of the excised specimens will lack histologically confirmed CIN.[71,72] Therefore this approach appears to be most appropriate for patients from populations at risk of loss to follow-up and for older pa-

tients in whom possible adverse effects of LEEP on fertility are not an issue.

### Recommendations for Managing Women With HSIL

Colposcopy with endocervical assessment is the recommended management of women with HSIL (AII). Subsequent management options depend on whether a lesion is identified, whether the colposcopic examination is satisfactory, whether the patient is pregnant, and whether immediate excision is appropriate.

**Satisfactory Colposcopy.** When no lesion or only biopsy-confirmed CIN 1 is identified after satisfactory colposcopy in women with HSIL, it is recommended that, when possible, a review of the cytology, colposcopy, and histology results be performed (BIII). If the review yields a revised interpretation, management should follow guidelines for the revised interpretation; if a cytological interpretation of HSIL is upheld or if review is not possible, a diagnostic excisional procedure is preferred in nonpregnant patients (BII). A colposcopic reevaluation with endocervical assessment is acceptable in special circumstances (see below) (BIII).

**Unsatisfactory Colposcopy.** When no lesion is identified after unsatisfactory colposcopy in women with HSIL, a review of the cytology, colposcopy, and histology results should be performed when possible (BIII). If the review yields a revised interpretation, management should follow guidelines for the revised interpretation. If a cytological interpretation of HSIL is upheld, review is not possible, or biopsy-confirmed CIN 1 is identified, a diagnostic excisional procedure is recommended in nonpregnant patients (AII). Ablation is unacceptable (EII).

Omission of endocervical sampling is acceptable when a diagnostic excisional procedure is planned. In women with HSIL in whom colposcopy suggests a high-grade lesion, initial evaluation using a diagnostic excisional procedure is also an acceptable option (BI). Triage using either a program of repeat cytological testing or HPV DNA testing is unacceptable (EII). Women with HSIL who are found to have biopsy-confirmed CIN should be managed according the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities (Wright et al, unpublished data, 2001).

### HSIL in Special Circumstances

**Pregnant Women.** It is preferred that the colposcopic evaluation of pregnant women with HSIL be conducted by clinicians who are experienced in the evaluation of colposcopic changes induced by pregnancy (BIII). Biopsy of lesions suspicious for high-grade disease or cancer is preferred; biopsy of other lesions is acceptable (BIII). Endocervical curettage is unacceptable in pregnant women (EIII). Since unsatisfactory colposcopy may become satisfactory as the pregnancy progresses, it is recommended that women with unsatisfactory colposcopic findings undergo a repeat colposcopic examination in 6 to 12 weeks (BIII). In the absence of invasive disease, additional colposcopic and cytological examinations are recommended, with biopsy recommended only if the appearance of the lesion worsens or if cytology suggests invasive cancer (BII). Unless invasive cancer is identified, treatment is unacceptable (EII). A diagnostic excisional procedure is recommended only if invasion is suspected (BII). Reevaluation with cytology and colposcopy is recommended no sooner than 6 weeks postpartum (CIII).

**Young Women of Reproductive Age.** When biopsy-confirmed CIN 2,3 is not identified in a young woman with cytology-confirmed HSIL, observation with colposcopy and cytology at 4- to 6-month intervals for 1 year is acceptable, provided colposcopic findings are satisfactory, endocervical sampling is negative, and the patient accepts the risk of occult disease. If a lesion appears to progress to a colposcopic high-grade lesion or if HSIL cytology persists, a diagnostic excisional procedure is recommended (BIII).

**Financial Disclosures:** Dr Wright was the principal investigator of clinical trials investigating HPV DNA testing and liquid-based cytology, funded by Digene Corp and Cytyc Corp via formal grants to Columbia University. Dr Wright has no financial or equity interest in, ongoing consultancy with, or membership on the scientific advisory board of Digene Corp, which makes the only FDA-approved HPV DNA test in the United States. Dr Wright currently serves on the speakers bureaus of Cytyc Corp and Tripath Inc, makers of liquid-based cytology test kits. Dr Cox has previously consulted for Digene Diagnostics and has been on the Digene speakers bureau. He is also a consultant for 3M Pharmaceuticals, Cytyc Corp, and Merck, and is on the speakers bureau for 3M Pharmaceuticals and Cytyc Corp. He has no other financial interest in any company that might benefit from cervical screening guidelines. Dr Massad was formerly the principal investigator of a grant to the Hektoen Institute correlating cervical disease with fluorescence data for SpectRx Inc. Dr Twiggs currently serves on the speakers bureaus for Cytyc Corp and Tripath Inc. Dr Wilkinson serves as a consultant for SpectRx and Welch Allyn, and is on the speakers bureau of Cytyc Corp.

**Working Groups:** *ASCUS Working Group:* Thomas C. Wright, MD, Columbia University, New York, NY; Walter Kinney, MD, University of California, Davis, Permanente Medical Group, Sacramento, Calif; Barbara Apgar, MD, University of Michigan, Ann Arbor; Carmel Cohen, MD, Mount Sinai Medical Center, New York, NY; Hershel Lawson, MD, Centers for Disease Control and Prevention; Mark Schiffman, MD, MPH, National Cancer Institute, Bethesda, Md; Mark Sherman, MD, National Cancer Institute, Bethesda, Md; Pamela Stratton, MD, National Institutes of Child Health and Human Development, Rockville, Md; Cornelia Trimble, MD, Johns Hopkins University, Baltimore, Md; Leslie Walton, MD, University of North Carolina School of Medicine, Chapel Hill.
*AGUS Working Group:* J. Thomas Cox, MD, University of California, Santa Barbara; R. Marshall Austin, MD, PhD, Medical University of South Carolina, Charleston; Raheela Ashfaq, MD, University of Texas Southwestern, Dallas; Francisco Garcia, MD, MPH, University of Arizona Health Sciences Center, Tucson; Diane Harper, MD, MPH, Dartmouth-Hitchcock Medical Center, Hanover, NH; Kenneth Noller, MD, Tufts New England Medical Center, Boston, Mass; Thomas Purdon, MD, University of Arizona Health Sciences Center, Tucson; Ellen Sheets, MD, Brigham and Women's Hospital, Boston, Mass; Ted Trimble, MD, MPH, National Cancer Institute, Bethesda, Md; Ralph Richart, MD, Columbia University, New York, NY; V. Cecil Wright, MD, University of Western Ontario, London.
*LSIL Working Group:* Edward Wilkinson, MD, University of Florida College of Medicine, Gainesville; Kenneth Hatch, MD, Arizona Cancer Center, Tucson; Marluce Bibbo, MD, Thomas Jefferson University Hospital, Philadelphia, Pa; Terrance Colgan, MD, Mount Sinai Hospital, Toronto, Ontario; Terri Cornelison, MD, National Cancer Institute, Bethesda, Md; Daron Ferris, MD, Medical College of Georgia, Augusta; Edward Partridge, MD, University of Alabama at Birmingham; Mark Spitzer, MD, North Shore University Hospital, Manhasset, NY; Claudia Werner, MD, University of Texas Southwestern, Dallas; Alan Waxman, MD, University of New Mexico, Albuquerque.
*HSIL Working Group:* Leo Twiggs, MD, University of Miami School of Medicine, Miami, Fla; Jay Carlson, DO, Walter Reed Army Medical Center, Washington, DC; J. L. Benedet, MD, British Columbia Cancer Agency, Vancouver; Christopher P. Crum, MD, Harvard Medical School, Boston, Mass; Juan Felix, MD, LAC-USC Medical Center, Los Angeles, Calif; Verda Hunter, MD, Resource Center for Gynecologic Oncology, Kansas City, Mo; Burton Krumholz, MD, Long Island Jewish Medical Center, Long Island, NY; Neal Lonky, MD, MPH, Kaiser Permanente, Yorba Linda, Calif; Stu Massad, MD, Cook County Hospital, Chicago, Ill; Luis Padilla, MD, University of New Mexico, Albuquerque.

**Financial Disclosures** for the working group members are available at: http://jama.ama-assn.org.

**Participants and Participating Organizations**

*Organizer:* American Society for Colposcopy and Cervical Pathology (ASCCP)

*Participants:* Fadi Abdul-Karim, MD, University Hospitals of Cleveland, Cleveland, Ohio; Barbara Bennett, MD, University of Florida, Gainesville; Guy Benrubi, MD, University of Florida at Jacksonville; Jonathan Berek, MD, UCLA School of Medicine, Los Angeles, Calif; Christine Bergeron, MD, Laboratoire Pasteur-CERBA, Paris, France; Monique Bertrand, MD, Vancouver Hospital and Health Sciences Center, Vancouver, British Columbia; George Birdsong, MD, Emory University, Atlanta, Ga; Patricia Braly, MD, Lakeside Hospital, New Orleans, La; Henry Buck, MD, University of Kansas, Lawrence; Louis Burke, MD, Beth Israel/Deaconess Medical Center, Harvard Medical School, Boston, Mass; David Chhieng, MD, University of Alabama, Birmingham; Edmund Cibas, MD, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass; William Creasman, MD, Medical University of South Carolina, Charleston; Teresa Darragh, MD, University of California, San Francisco; Diane Davey, MD, University of Kentucky, Lexington; Santiago Dexeus, MD, Institut Universitari Dexeus, Barcelona, Spain; Charles Dunton, MD, Thomas Jefferson University Hospital, Philadelphia, Pa; Paul Elgert, CT, New York University School of Medicine, New York, NY; Alex Ferenczy, MD, McGill University, Sir Mortimber B. Davis Jewish Central Hospital, Montreal, Quebec; Catterina Ferreccio, MD, MPH, Pan American Health Organization, Washington, DC; Lisa Flowers, MD, Emory University, Atlanta, Ga; William Frable, MD, Virginia Commonwealth University, Richmond; Joseph Fraumeni, National Cancer Institute, Bethesda, Md; Robert Gay, CT, APL School of Cytotechnology, Las Vegas, Nev; Melvin Gerbie, MD, Northwestern University Medical School, Chicago, Ill; Sue Goldie, MD, MPH, Harvard Center for Risk Analysis, Boston, Mass; Ben Greer, MD, University of Washington Medical Center, Seattle; Richard Guido, MD, Magee Women's Hospital, Pittsburgh, Pa; Fernando Guijon, MD, University of Manitoba, Winnipeg; Hope Haefner, MD, University of Michigan, Ann Arbor; Vivien Hanson, MD, University of Washington, Seattle; Michael Henry, MD, University of Maryland, Baltimore; Robert Hilgers, MD, University of Louisville, Louisville, Ky; Angela Houghton, MD, American Medical Women's Association, Alexandria, Va; Lydia Howell, MD, University of California, Davis; Martha Hutchinson, MD, PhD, Tiverton, RI; Howard W. Jones III, MD, Vanderbilt University, Nashville, Tenn; Thomas M. Julian, MD, University of Wisconsin, Madison; Raymond H. Kaufman, MD, Baylor School of Medicine, Houston, Tex; Gordon M. Lickrish, MD, University of Toronto, Toronto, Ontario; Louise Magruder, US Food and Drug Administration, Rockville, Md; Edward J. Mayeaux, MD, Louisiana State University Health Sciences Center, Shreveport; Dennis McCoy, Esq, Saperston & Day, PC, Buffalo, NY; Larry McGowan, MD, George Washington University, Washington, DC; Kathy McIntyre-Seltman, MD, Magee Women's Hospital, Pittsburgh, Pa; James McNeil, Jr, MD, Naval Hospital, Jacksonville, Fla; Joseph Monsonego, MD, Eurogin, Paris, France; Ann Moriarty, MD, AmeriPath Indiana, Indianapolis; Anna-Barbara Moscicki, MD, University of California, San Francisco; Joan Murphy, Princess Margaret Hospital, Toronto, Ontario; Dennis O'Connor, MD, University of Louisville School of Medicine, Louisville, Ky; Marianne U. Prey, MD, Quest Diagnostics, Inc, St Louis, Mo; Stephen Raab, MD, Allegheny General Hospital, Pittsburgh, Pa; Max Robinowitz, MD, US Food and Drug Administration, Rockville, Md; Dorothy Rosenthal, MD, Johns Hopkins University, Baltimore, Md; Michel Roy, MD, Laval University, Quebec City, Quebec; Mary Rubin, PhD, CRNP, Education Programs Associates, Sausalito, Calif; Carolyn Runowicz, MD, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY; Michael Shier, MD, University of Toronto, Toronto, Ontario; Mary Sidawy, MD, George Washington University, Washington, DC; Albert Singer, MD, Whittington Hospital, London, England; Robert Smith, PhD, American Cancer Society, Atlanta, Ga; Diane Solomon, National Cancer Institute, Bethesda, Md; Gerald Stanimir, Royal Victoria Hospital, Montreal, Quebec; Mark Stoler, MD, University of Virginia Health Sciences Center, Charlottesville; Sana Tabbara, MD, George Washington University, Washington, DC; Jeffrey Waldman, MD, Planned Parenthood Shasta-Diablo, Concord, Calif; Eric Wall, MD, MPH, Premera Blue Cross, Oregon Health Sciences University, Portland; Joan Walker, MD, University of Oklahoma, Oklahoma City; Bethany Weaver, DO, University of Washington, Seattle; Edward Wiesmeier, MD, UCLA, Los Angeles, Calif; Dorothy Wiley, PhD, UCLA School of Nursing, Los Angeles, Calif; Gerald Willett, MD, US Food and Drug Administration, Rockville, Md; Barbara Winkler, MD, Quest Diagnostics Inc, Tetenboro, NJ; Cheryl Wiseman, MPH, CT, Centers for Medicaid and Medicare Services, Baltimore, Md; Susan Wysocki, RNC, NP, National Association for Nurse Practitioners in Women's Health, Washington, DC; Nancy Young, MD, Fox Chase Cancer Center, Philadelphia, Pa; Lauren Zoschnick, MD, University of Michigan, Ann Arbor; Rosemary Zuna, MD, University of Oklahoma Health Sciences Center, Oklahoma City.

*Participating Organizations:* Agency for Healthcare Research and Quality, American Academy of Family Physicians, American Cancer Society, American College Health Association, American College of Obstetricians and Gynecologists, American Medical Women's Association, American Social Health Association, American Society for Clinical Pathologists, American Society for Colposcopy and Cervical Pathology, American Society of Cytopathology, Association of Reproductive Health Professionals, Centers for Disease Control and Prevention, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Division of Laboratory Systems, Centers for Medicaid and Medicare Services, College of American Pathologists, Eurogin, Food and Drug Administration, International Academy of Cytology, International Federation for Cervical Pathology and Colposcopy, International Gynecologic Cancer Society, International Society of Gynecological Pathologists, National Cancer Institute, National Association of Nurse Practitioners in Women's Health, Papanicolaou Society, Pan American Health Organization, Planned Parenthood Federation of America, Society of Canadian Colposcopists, Society of Gynecologic Oncologists, Society of Obstetricians & Gynaecologists of Canada.

**Acknowledgment:** We thank Kathy Poole for administrative support during the development of the guidelines. These guidelines were developed with support from the American Society of Colposcopy and Cervical Pathology and by National Cancer Institute grant 1 R13 CA 96190-01. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

## REFERENCES

**1.** Jones HW. The Bethesda System. *Cancer*. 1995; 76(suppl):1914-1918.
**2.** Jones BA, Davey DD. Quality management in gynecologic cytology using interlaboratory comparison. *Arch Pathol Lab Med*. 2000;124:672-681.
**3.** Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA*. 2002;287:2114-2119.
**4.** Manos MM, Kinney WK, Hurley LB, et al. Identifying women with cervical neoplasia. *JAMA*. 1999; 281:1605-1610.
**5.** Wright TC Jr, Lorincz A, Ferris DG, et al. Reflex human papillomavirus deoxyribonucleic acid testing in women with abnormal Papanicolaou smears. *Am J Obstet Gynecol*. 1998;178:962-966.
**6.** US Public Health Service (USPHS), Infectious Diseases Society of America (IDSA). 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR Recomm Rep*. 1999;48(RR-10): 1-59, 61-66.
**7.** Kish MA. Guide to development of practice guidelines. *Clin Infect Dis*. 2001;32:851-854.
**8.** Wright TC, Ferenczy AF, Kurman RJ. Precancerous lesions of the cervix. In: Kurman RJ, ed. *Blaustein's Pathology of the Female Genital Tract*. 4th ed. New York, NY: Springer-Verlag; 1994:229-278.
**9.** Robb JA. The "ASCUS" swamp. *Diagn Cytopathol*. 1994;11:319-320.
**10.** Sherman ME, Schiffman MH, Lorincz AT, et al. Toward objective quality assurance in cervical cytopathology. *Am J Clin Pathol*. 1994;102:182-187.
**11.** Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations. *JAMA*. 2001;285:1500-1505.
**12.** Solomon D, Schiffman M, Tarrone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance. *J Natl Cancer Inst*. 2001;93:293-299.
**13.** Slawson DC, Bennett JH, Simon LJ, Herman JM, for the Harrisburgh Area Research Network. Should all women with cervical atypia be referred for colposcopy: a HARNET study. *J Fam Pract*. 1994;38:387-392.
**14.** Kobelin MH, Kobelin CG, Burke L, Lavin P, Niloff JM, Kim YB. Incidence and predictors of cervical dysplasia in patients with minimally abnormal Papanicolaou smears. *Obstet Gynecol*. 1998;92:356-359.
**15.** Eskridge C, Begneaud WP, Landwehr C. Cervicography combined with repeat Papanicolaou test as triage for low-grade cytologic abnormalities. *Obstet Gynecol*. 1998;92:351-355.
**16.** Crum CP, Genest DR, Krane JF, et al. Subclassifying atypical squamous cells in Thin-Prep cervical cytology correlates with detection of high-risk human papillomavirus DNA. *Am J Clin Pathol*. 1999;112:384-390.
**17.** Schoolland M, Sterrett GF, Knowles SA, Mitchell KM, Kurinczuk JJ. The "Inconclusive—possible high grade epithelial abnormality" category in Papanicolaou smear reporting. *Cancer*. 1998;84:208-217.
**18.** Malik SN, Wilkinson EJ, Drew PA, Bennett BB, Hardt NS. Do qualifiers of ASCUS distinguish between low- and high-risk patients? *Acta Cytol*. 1999; 43:376-380.
**19.** Sherman ME, Solomon D, Schiffman M. Qualification of ASCUS: a comparison of equivocal LSIL and equivocal HSIL cervical cytology in the ASCUS LSIL Triage Study (ALTS). *Am J Clin Pathol*. In press.
**20.** Quddus MR, Sung CJ, Steinhoff MM, Lauchlan SC, Singer DB, Hutchinson ML. Atypical squamous metaplastic cells. *Cancer*. 2001;93:16-22.
**21.** Jones BA, Novis DA. Follow-up of abnormal gynecologic cytology: a college of American pathologists Q-probes study of 16132 cases from 306 laboratories. *Arch Pathol Lab Med*. 2000;124:665-671.
**22.** Lonky NM, Sadeghi M, Tsadik GW, Petitti D. The clinical significance of the poor correlation of cervical dysplasia and cervical malignancy with referral cytologic results. *Am J Obstet Gynecol*. 1999;181: 560-566.
**23.** Wright TC, Moscarelli RD, Dole P, Ellerbrock TV, Chiasson MA, Vandevanter N. Clinical significance of mild cytologic atypia on Papanicolaou smears from women infected with human immunodeficiency virus. *Obstet Gynecol*. 1996;87:515-519.
**24.** Sun XW, Kuhn L, Ellerbrock TV, Chiasson MA, Wright TC. Human papillomavirus infection in HIV-seropositive women. *N Engl J Med*. 1997;337:1343-1349.
**25.** Keating JT, Wang HH. Significance of a diagnosis of atypical squamous cells of undetermined significance for Papanicolaou smears in perimenopausal and postmenopausal women. *Cancer*. 2001;93:100-105.
**26.** Flynn K, Rimm DL. Diagnosis of "ASCUS" in women over age 50 is less likely to be associated with dysplasia. *Diagn Cytopathol*. 2001;24:132-136.
**27.** Bergeron C, Jeannel D, Poveda J, Cassonnet P, Orth

G. Human papillomavirus testing in women with mild cytologic atypia. *Obstet Gynecol*. 2000;95:821-827.
**28.** Ferris DG, Wright TC Jr, Litaker MS, et al. Comparison of two tests for detecting carcinogenic HPV in women with Papanicolaou smear reports of ASCUS and LSIL. *J Fam Pract*. 1998;46:136-141.
**29.** Lin CT, Tseng CJ, Lai CH, Hsueh S, Huang HJ, Law KS. High-risk HPV DNA detection by Hybrid Capture II. *J Reprod Med*. 2000;45:345-350.
**30.** Shlay JC, Dunn T, Byers T, Baron AE, Douglas JM Jr. Prediction of cervical intraepithelial neoplasia grade 2-3 using risk assessment and human papillomavirus testing in women with atypia on papanicolaou smears. *Obstet Gynecol*. 2000;96:410-416.
**31.** Kurman RJ, Henson DE, Herbst AL, Noller KL, Schiffman MH. Interim guidelines for management of abnormal cervical cytology. *JAMA*. 1994;271:1866-1869.
**32.** Cox JT, Wilkinson EJ, Lonky N, Waxman A, Tosh R, Tedeschi C. Management guidelines for the follow-up of atypical squamous cells of undetermined significance (ASCUS). *J Lower Gen Tract Dis*. 2000; 4:99-105.
**33.** American College of Obstetricians and Gynecologists. *Cervical Cytology: Evaluation and Management of Abnormalities*. Washington, DC: American College of Obstetricians and Gynecologists; 1993: 1-7. ACOG Techical Bulletin 183.
**34.** Cox T, Lorincz AT, Schiffman MH, Sherman ME, Cullen A, Kurman RJ. Human papillomavirus testing by hybrid capture appears to be useful in triaging women with a cytologic diagnosis of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol*. 1995;172:946-954.
**35.** Ferris DG, Wright TC Jr, Litaker MS, et al. Triage of women with ASCUS and LSIL on Pap smear reports. *J Fam Pract*. 1998;46:125-134.
**36.** Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol*. 1998;91:626-631.
**37.** Sherman ME, Schiffman M, Cox JT, Group TA. Effects of age and human papilloma viral load on colposcopy triage. *J Natl Cancer Inst*. 2002;94:102-107.
**38.** Ronnett BM, Manos MM, Ransley JE, et al. Atypical glandular cells of undetermined significance (AGUS). *Hum Pathol*. 1999;30:816-825.
**39.** Kennedy AW, Salmieri SS, Wirth SL, Biscotti CV, Tuason LJ, Travarca MJ. Results of the clinical evaluation of atypical glandular cells of undetermined significance (AGCUS) detected on cervical cytology screening. *Gynecol Oncol*. 1996;63:14-18.
**40.** Valdini A, Vaccaro C, Pechinsky G, Abernathy V. Incidence and evaluation of an AGUS Papanicolaou smear in primary care. *J Am Board Fam Pract*. 2001; 14:172-177.
**41.** Duska LR, Flynn CF, Chen A, Whall-Strojwas D, Goodman A. Clinical evaluation of atypical glandular cells of undetermined significance on cervical cytology. *Obstet Gynecol*. 1998;91:278-282.
**42.** Taylor RR, Guerrieri JP, Nash JD, Henry MR, O'Connor DM. Atypical cervical cytology: colposcopic follow-up using the Bethesda System. *J Reprod Med*. 1993;38:443-447.
**43.** Goff BA, Atanasoff P, Brown E, Muntz HG, Bell DA, Rice LW. Endocervical glandular atypia in Papanicolaou smears. *Obstet Gynecol*. 1992;79:101-104.
**44.** Zweizig S, Noller K, Reale F, Collis S, Resseguie L. Neoplasia associated with atypical glandular cells of undetermined significance on cervical cytology. *Gynecol Oncol*. 1997;65:314-318.
**45.** Soofer SB, Sidawy MK. Atypical glandular cells of undetermined significance. *Cancer*. 2000;90:207-214.
**46.** Eddy GL, Wojtowycz MA, Piraino PS, Mazur MT. Papanicolaou smears by the Bethesda system in endometrial malignancy. *Obstet Gynecol*. 1997;90:999-1003.
**47.** Veljovich DS, Stoler MH, Andersen WA, Covell JL, Rice LW. Atypical glandular cells of undetermined significance. *Am J Obstet Gynecol*. 1998;179:382-390.
**48.** Chhieng DC, Elgert P, Cohen JM, Cangiarella JF. Clinical significance of atypical glandular cells of undetermined significance in postmenopausal women. *Cancer*. 2001;93:1-7.
**49.** Laverty CR, Farnsworth A, Thurloe J, Bowditch R. The reliability of a cytological prediction of cervical adenocarcinoma in situ. *Aust N Z J Obstet Gynaecol*. 1988;28:307-312.
**50.** Lee KR, Manna EA, St John T. Atypical endocervical glandular cells: accuracy of cytologic diagnosis. *Diagn Cytopathol*. 1995;13:202-208.
**51.** Mitchell H, Medley G, Gordon I, Giles G. Cervical cytology reported as negative and risk of adenocarcinoma of the cervix. *Br J Cancer*. 1995;71:894-897.
**52.** Kim TJ, Kim HS, Park CT, et al. Clinical evaluation of follow-up methods and results of atypical glandular cells of undetermined significance (AGUS) detected on cervicovaginal pap smears. *Gynecol Oncol*. 1999;73:292-298.
**53.** Lee KR, Minter LJ, Granter SR. Papanicolaou smear sensitivity for adenocarcinoma in situ of the cervix: a study of 34 cases. *Am J Clin Pathol*. 1997;107:30-35.
**54.** Krane JF, Granter SR, Trask CE, Hogan CL, Lee KR. Papanicolaou smear sensitivity for the detection of adenocarcinoma of the cervix: a study of 49 cases. *Cancer*. 2001;93:8-15.
**55.** Cullimore JE, Luesley DM, Rollason TP, et al. A prospective study of conization of the cervix in the management of cervical intraepithelial glandular neoplasia (CIGN): a preliminary report. *Br J Obstet Gynaecol*. 1992;99:314-318.
**56.** Denehy TR, Gregori CA, Breen JL. Endocervical curettage, cone margins, and residual adenocarcinoma in situ of the cervix. *Obstet Gynecol*. 1997;90:1-6.
**57.** Wolf JK, Levenback C, Malpica A, Morris M, Burke T, Mitchell MF. Adenocarcinoma in situ of the cervix. *Obstet Gynecol*. 1996;88:82-86.
**58.** Kinney WK, Manos MM, Hurley LB, Ransley JE. Where's the high-grade cervical neoplasia? *Obstet Gynecol*. 1998;91:973-976.
**59.** Geier CS, Wilson M, Creasman W. Clinical evaluation of atypical glandular cells of undetermined significance. *Am J Obstet Gynecol*. 2001;184:64-69.
**60.** Chin AB, Bristow RE, Korst LM, Walts A, Lagasse LD. The significance of atypical glandular cells on routine cervical cytologic testing in a community-based population. *Am J Obstet Gynecol*. 2000;182:1278-1282.
**61.** Ostor AG, Duncan A, Quinn M, Rome R. Adenocarcinoma in situ of the uterine cervix: an experience with 100 cases. *Gynecol Oncol*. 2000;79:207-210.
**62.** Widrich T, Kennedy AW, Myers TM, Hart WR, Wirth S. Adenocarcinoma in situ of the uterine cervix. *Gynecol Oncol*. 1996;61:304-308.
**63.** Muntz HG, Bell DA, Lage JM, Goff BA, Feldman S, Rice LW. Adenocarcinoma in situ of the uterine cervix. *Obstet Gynecol*. 1992;80:935-939.
**64.** Cox JT. ASCCP Practice Guidelines: management of glandular abnormalities in the cervical smear. *J Lower Gen Tract Dis*. 1997;1:41-45.
**65.** Azodi M, Chambers SK, Rutherford TJ, Kohorn EI, Schwartz PE, Chambers JT. Adenocarcinoma in situ of the cervix. *Gynecol Oncol*. 1999;73:348-353.
**66.** Takezawa K, Bennett BB, Wilkinson EJ, Drew PA, Hardt NS. Squamous intraepithelial lesions of the cervix in a high-risk population. *J Lower Gen Tract Dis*. 1998;2:136-140.
**67.** Robertson JH, Woodend B, Elliott H. Cytological changes preceding cervical cancer. *J Clin Pathol*. 1994; 47:278-279.
**68.** Robertson JH, Woodend BE, Crozier EH, Hutchinson J. Risk of cervical cancer associated with mild dyskaryosis. *BMJ*. 1988;297:18-21.
**69.** Kirby AJ, Spiegelhalter DJ, Day NE, et al. Conservative treatment of mild/moderate cervical dyskaryosis: long-term outcome. *Lancet*. 1992;339:828-831.
**70.** Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions. *J Natl Cancer Inst*. 2000;92:397-402.
**71.** Bigrigg MA, Codling BW, Pearson P, Read MD, Swingler GR. Colposcopic diagnosis and treatment of cervical dysplasia at a single clinic visit. *Lancet*. 1990; 336:229-231.
**72.** Luesley DM, Cullimore J, Redman CWE, et al. Loop diathermy excision of the cevical transformation zone in patients with abnormal cervical smears. *BMJ*. 1990; 300:1690-1693.
**73.** Howells RE, O'Mahony F, Tucker H, Millinship J, Jones PW, Redman CW. How can the incidence of negative specimens resulting from large loop excision of the cervical transformation zone (LLETZ) be reduced? *Br J Obstet Gynaecol*. 2000;107:1075-1082.
**74.** Spitzer M, Chernys AE, Shifrin A, Ryskin M. Indications for cone biopsy: pathologic correlation. *Am J Obstet Gynecol*. 1998;178:74-79.
**75.** Massad LS, Collins YC, Meyer PM. Biopsy correlates of abnormal cervical cytology classified using the Bethesda system. *Gynecol Oncol*. 2001;82:516-522.
**76.** Jones BA, Novis DA. Cervical biopsy-cytology correlation: a College of American Pathologists Q-Probes study of 22 439 correlations in 348 laboratories. *Arch Pathol Lab Med*. 1996;120:523-531.
**77.** Brown FM, Faquin WC, Sun D, Crum CP, Cibas ES. LSIL biopsies after HSIL smears. *Am J Clin Pathol*. 1999;112:765-768.
**78.** Chappatte OA, Byrne DL, Raju KS, Nayagam M, Kenney A. Histological differences between colposcopic-directed biopsy and loop excision of the transformation zone (LETZ). *Gynecol Oncol*. 1991;43:46-50.
**79.** Milne DS, Wadehra V, Mennim D, Wagstaff TI. A prospective follow up study of women with colposcopically unconfirmed positive cervical smears. *Br J Obstet Gynaecol*. 1999;106:38-41.
**80.** Grenko RT, Abendroth CS, Frauenhoffer EE, Ruggiero FM, Zaino RJ. Variance in the interpretation of cervical biopsy specimens obtained for atypical squamous cells of undetermined significance. *Am J Clin Pathol*. 2000;114:735-740.
**81.** Joste NE, Rushing L, Granados R, et al. Bethesda classification of cervicovaginal smears: reproducibility and viral correlates. *Hum Pathol*. 1996;27:581-585.
**82.** Benedet JL, Selke PA, Nickerson KG. Colposcopic evaluation of abnormal Papanicolaou smears in pregnancy. *Am J Obstet Gynecol*. 1987;157:932-937.
**83.** Economos K, Perez Veridiano N, Delke I, Collado ML, Tancer ML. Abnormal cervical cytology in pregnancy: a 17-year experience. *Obstet Gynecol*. 1993;81:915-918.
**84.** Woodrow N, Permezel M, Butterfield L, Rome R, Tan J, Quinn M. Abnormal cervical cytology in pregnancy. *Aust N Z J Obstet Gynaecol*. 1998;38:161-165.
**85.** Bigrigg A, Haffenden DK, Sheehan AL, Codling BW, Read MD. Efficacy and safety of large-loop excision of the transformation zone. *Lancet*. 1994;343:32-34.
**86.** Denny LA, Soeters R, Dehaeck K, Bloch B. Does colposcopically directed punch biopsy reduce the incidence of negative LLETZ? *Br J Obstet Gynaecol*. 1995;102:545-548.
**87.** Holschneider CH, Felix JC, Satmary W, Johnson MT, Sandweiss LM, Montz FJ. A single-visit cervical carcinoma prevention program offered at an inner city church: a pilot project. *Cancer*. 1999;86:2659-2667.
**88.** Santos C, Galdos R, Alvarez J, et al. One-session management of cervical intraepithelial neoplasia. *Gynecol Oncol*. 1996;61:11-15.
**89.** Gross PA, Barrett TL, Dellinger EP, et al, for the Infectious Diseases Society of America. Purpose of quality standards for infectious diseases. *Clin Infect Dis*. 1994;18:421.

## *Definitions of Terms Utilized in the Consensus Guidelines*

***Colposcopy*** is the examination of the cervix, vagina, and, in some instances the vulva, with the colposcope after the application of a 3-5% acetic acid solution coupled with obtaining colposcopically-directed biopsies of all lesions suspected of representing neoplasia.

***Endocervical sampling*** includes obtaining a specimen for either histological evaluation using an endocervical curette or a cytobrush or for cytological evaluation using a cytobrush.

***Endocervical assessment*** is the process of evaluating the endocervical canal for the presence of neoplasia using either a colposcope or endocervical sampling.

***Diagnostic excisional procedure*** is the process of obtaining a specimen from the transformation zone and endocervical canal for histological evaluation and includes laser conization, cold-knife conization, loop electrosurgical excision (i.e., LEEP), and loop electrosurgical conization.

***Satisfactory colposcopy*** indicates that the entire squamocolumnar junction and the margin of any visible lesion can be visualized with the colposcope.

***Endometrial sampling*** includes obtaining a specimen for histological evaluation using an endometrial biopsy or a “dilatation and curettage” or hysteroscopy.

**Financial Disclosures for Working Group Members:** Dr Apgar has served on the speakers bureau of TriPath Imaging Inc; Dr Ashfaq has received honoraria and travel expenses for lectures from Cytyc Corp; Dr Austin has been a speaker or consultant without personal compensation for AutoCyte Inc, Cytyc, Digene Corp, Morphometrics, NeoPath Inc, Neuromedical Sciences Inc, and Veracel Inc; Dr Colgan has been a principal investigator for NeoPath and AutoCyte, and has served as a consultant for Veracel; Dr Ferris has received honoraria from Cytyc and Digene, grants from Cytyc, and has served as a consultant for Digene; Dr Garcia has received research supplies from Cytyc and Digene, but has no financial interest in either; Dr Hunter has served on the speakers bureau of USHealthConnect and has served as principal investigator for a pilot study from LifeSpex Inc; Dr Kinney has received laboratory support and supplies from Cytyc and Digene (ending in 1997) for a study of ASCUS, and has served on the speakers bureaus of Cytyc and Digene; Dr Krumholz has served on the speakers bureau of Cytyc; Dr Lonky is the Chairman of the Medical Advisory Board of, and is a shareholder and Director of, Trylon Corp, and has served on the speakers bureau of 3M Corp; Dr Richart has served on the speakers bureaus of Cytyc and Digene, and is a shareholder of Digene common stock; Dr Sheets has served on the speakers bureau of Cytyc; Dr Sherman has received research support from Cytyc and Digene; Dr Spitzer has served on the speakers bureaus of 3M, Cytyc, and USHealthConnect, and has received research support from Polartechnics Corp; Dr Walton owns shares of Cytyc, and has received a Pap smear grant funded by Digene.